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Familial Recurrence of Tracheoesophageal Fistula and Associated Malformations

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Tracheoesophageal fistula (TEF) may occur as an isolated malformation or together with other malformations. To determine the recurrence risk of TEF or associated malformations in children and sibs, and to determine the frequency of associated malformations in index patients, we reviewed the Mayo Clinic records of 204 patients with TEF. Also, questionnaires were sent to patients or relatives. Questions were designed to determine whether the patient and relatives had TEF and/or related organ system (including VACTERL) malformations. The VACTERL association is a disorder characterized by 3 or more of the following: vertebral, anal, cardiac, renal, or radial anomalies, and TEF. One hundred twenty-eight families returned a completed questionnaire, and 140 index patients were ascertained based on complete medical records, questionnaire, and/or autopsy. Forty-one (29.3%) of 140 index patients had TEF with one other VACTERL malformation, and twenty-four (17.1%) of 140 index patients had TEF with at least two other VACTERL malformations. Of the 347 sibs of index patients, 5 (1.4%) had one VACTERL malformation each, including 1 sib with esophageal atresia (EA) without TEF. Of the 41 children of index patients, 1 (2.4%) had TEF plus two other VACTERL malformations; another had one non-TEF VACTERL malformation. From our study, the largest reported population of TEF patients to date, we conclude that: 1) nearly half (46%) of patients with tracheoesophageal fistula will exhibit other VACTERL malformations; 2) the recurrence risk for individuals with TEF to have affected children is 2–3%; and 3) there is an increased risk to relatives of TEF patients to exhibit other VACTERL malformations.

KEY WORDS: tracheoesophageal fistula, VATER/VACTERL association, trachea malformation

INTRODUCTION

Congenital tracheoesophageal fistula is a malformation of unknown etiology which occurs in an estimated 1 in 3,000 live births [Warren et al., 1979; David and O'Callaghan, 1975]. The most common form of tracheoesophageal fistula (TEF) is esophageal atresia (EA) with TEF between the lower esophagus and trachea (85–95%). Other types of esophageal malformations include: 1) esophageal atresia without TEF; 2) TEF without EA; 3) EA with fistula between the upper esophageal segment and trachea; 4) fistula from the lower esophageal segment to a main stem bronchus; and 5) EA with fistula from both upper and lower esophageal segments of the trachea [Belknap, 1990; Gray and Skandalakis, 1972]. TEF can occur as an isolated malformation, but often occurs as part of the VACTERL association [Barnes and Smith, 1978; Quan and Smith, 1973]. VACTERL is an acronym used to describe the nonrandom association of the following malformations: vertebral and vascular (V); anorectal (A); cardiac (C); tracheoesophageal fistula and esophageal atresia (TE); renal (R); and limb (L). TEF has been described in association with many chromosome abnormalities and malformation syndromes, including trisomy 21, trisomy 18, 13q−, 4p−, CHARGE "association," Goldenhar anomaly, DiGeorge sequence, Robin sequence, and Holt-Oram syndrome. TEF has also been reported as a finding in a number of case reports of patients with multiple malformations [Siegler et al., 1980; Blaichman, 1982; Currarino and Friedman, 1986; Konig et al., 1990; Bixler and Antley, 1974; Mehes, 1984; Hodson and Shaw, 1973; Rogers, 1988; Rosenak et al., 1991; Duncan and Shapiro, 1988; Shackelford et al., 1973).

A review suggests that the recurrence risk for nonsyndromic TEF or isolated esophageal atresia is $< 1\%$ to sibs in families with one affected child [Warren et al., 1979; David and O'Callaghan, 1975; Chen et al., 1979;

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Skinner, 1990; Pletcher et al., 1991; Szendry et al., 1985; Briard et al., 1977]. The recurrence risk for an affected individual to have an affected child has been estimated to be between 2–4% [Warren et al., 1979; King et al., 1977; Pletcher et al., 1991]. However, only one study was specifically performed to determine accurate recurrence risks for TEF in children born to affected individuals. Although Warren et al. [1979] found that 15 patients with TEF had 28 children, of whom 1 was affected (3.6%), they concluded that the recurrence risk to children was about 1% for counseling purposes. TEF is thought to be multifactorial in origin, but a single genetic locus could be responsible for recurrence in some families. This study was undertaken to determine more accurate recurrence risks for TEF and VACTERL malformations, particularly for children born to affected parents, and to determine the frequency of VACTERL malformations in patients with TEF.

PATIENTS AND METHODS

We reviewed Mayo Clinic records of all patients with the diagnosis of congenital TEF who were evaluated at the Mayo Clinic between 1935–1990. Two hundred cases had the clinical diagnosis of congenital TEF. Mayo Clinic charts and autopsy reports of all patients were reviewed to confirm diagnosis of TEF and to determine whether associated malformations were present. A questionnaire was sent to the most recent address in the chart. Included in the questionnaire were questions designed to: 1) confirm the diagnosis of TEF in the index case; 2) note the occurrence of other VACTERL-associated malformations in the index case; and 3) obtain information on sibs, parents, and children regarding TEF and other VACTERL-associated malformations. Questionnaires returned due to antiquated addresses did occur, as a number of patients had not been seen at the Mayo Clinic in over 20 years. When questionnaires were not returned, one follow-up telephone call was made. If the patient was known to be deceased, the questionnaire was sent to parents or to a sib. If the patient was still a minor, the questionnaire was sent to parents or guardian. Information from the returned questionnaires was verified by review of medical records, autopsy report, or a follow-up telephone call.

RESULTS

We received 129 questionnaires of 200 sent out (64.5%). One of the returned questionnaires was a refusal, giving 128 completed questionnaires out of 200 (64%). Thirty-seven questionnaires were returned by the post office, and no other address or relative could be located. Thirty-four questionnaires were not returned, only 12 of which were sent to confirmed current addresses. If one considers only the 12 unreturned questionnaires that we believe were sent to current addresses, our response rate was 128 out of 141 (90.7%). This suggests that ascertainment bias based on response rate is unlikely or minimal. Several cases were discarded from analysis because other diagnoses existed, including Down syndrome, trisomy 18, Opitz-Frias syndrome, and Roussy-Levy syndrome. The diagnosis of congenital TEF was accepted if verified by surgery or autopsy. Enough data existed in the Mayo Clinic chart, in autopsy reports, and/or from questionnaires on 140 individuals to allow them to be designated as index cases and to determine whether other VACTERL anomalies were present in the index cases. All responses on questionnaires were verified by telephone. All index patients but one were born between 1943–1989; 76 of the 140 index cases were born after 1964. One living index patient was born in 1928, but diagnosed in 1979 with a congenital H-type TEF. Fifty-eight of the 140 index cases died after transfer to our institution, and 45 had complete autopsies. Seventy-eight of the 140 index cases were male (55%).

Forty-one of the 140 index cases had TEF with one other VACTERL malformation (29.3%). Twenty-four others had TEF with two or more VACTERL malformations (17.1%) (Table I). The most commonly-occurring other VACTERL malformations in the index patients were congenital heart defects, followed by renal, anorectal, vertebral, and radial ray malformations (Table II). Questionnaires allowed information to be determined regarding TEF and associated malformations on 252 biological parents. Four parents were unknown, since 2 patients had been adopted. Five parents of index patients had one malformation that can be associated with VACTERL: 3 were fathers, 2 were mothers. Four of these parents had renal anomalies (1 with malpositioned kidney, 1 with duplicated left kidney, and 2 with solitary kidney); the fifth parent had a congenital heart defect (bicuspid aortic valve). Thus, 5 of 252 biological parents (2%) had VACTERL-related malformations (Table III), although some of these malformations are common and could be coincidental.

Of 347 full sibs, 1 sib of a patient with esophageal atresia and TEF had esophageal atresia without TEF (0.3%). Three other sibs (0.9%), none from the same family, had a congenital heart defect (transposition of the great vessels, univentricular heart, and two-chambered heart). One additional sib had an unspecified solitary spinal abnormality (0.3%) (Table IV). Three of the index cases in our study were twins: 1 dizygotic, and 2 of unknown zygosity. All 3 patients were discordant for TEF and any VACTERL malformation. There were no TEF or VACTERL malformations in relatives in these three families.

Eighty-two of the 140 index patients are living; 23 of these individuals have had a total of 41 offspring. Information was obtained on all of these children. Of these, one was born with esophageal atresia with TEF (2.4%). This child also had a congenital heart defect and

TABLE I. TEF and VACTERL Malformations in Index Cases

	n (%)
TEF cases (questionnaire and/or autopsy)	140
Cases with TEF and no other VACTERL malformations	75 (53.6)
Cases with TEF and one other VACTERL malformation	41 (29.3)
Cases with TEF and two or more other VACTERL malformations	24 (17.1)

TABLE II. Incidence of Non-TEF VACTERL Malformations Among Index Cases

	n (%)
Total index cases	140
Congenital heart disease	34 (24.3)
Renal malformations	21 (15.0)
Vertebral malform,ations	15 (10.7)
Radial ray malformations	11 (7.9)
Rectal malformations/anal atresia	16 (11.4)

TABLE IV. Incidence of TEF and/or VACTERL Malformations in Sibs

	n (%)
Sibs	347
TEF-affected siblings	1 (0.3)
Sibs with spinal malformations	1 (0.3)
Sibs with congenital heart disease	3 (0.9)
Sibs with non-TEF VACTERL malformations	4 (1.2)
Sibs with no VACTERL malformations	342 (98.0)

a radial ray anomaly. One other child of a living index patient was born with a horseshoe kidney but no other VACTERL malformations. The remaining 39 children had no documented TEF or VACTERL malformations (Table V).

DISCUSSION

The rate of return of questionnaires (90.8%) was high when they were sent to current addresses. By including questions to determine whether the patient or relatives had TEF, we had hoped to determine the recurrence risk of congenital TEF to children. We also intended to determine the recurrence risk of congenital TEF in sibs and other first-degree relatives, and the frequency of other VACTERL malformations in the study groups. It has been proposed that TEF is multifactorial in origin, with the recurrence risk to offspring of affected individuals being quoted for genetic counseling purposes as approximately 1% [Skinner, 1990]. The origin of this number is unclear. From our series, the empiric recurrence risk of TEF to children is about 2.4% (95% confidence interval (CI), 0.6–12.9%). This series is larger than any previously reported. The current study was prompted by the presentation of our one family with a recurrence of TEF, and we therefore realize that there may be selection bias to our results. If this family is eliminated, there were no recurrences of TEF in our series of children born to affected parents. Thirty-nine of our 140 index patients were referred from towns more than 300 miles from Rochester. Most (82 of 140) traveled 200 or fewer miles from the referral institution. It is possible that some critically ill infants could not be transported, and that results from the earlier years of the study could have been biased on this basis. Comprehensive genetic evaluation was not available in the early years of the study; however, the inclusion of complete autopsies, completion of questionnaires on living and deceased patients, review of Mayo medical records, and the telephone interview should have detected any clinically significant additional malformations or congenital problems. Our study revealed a slight excess of males (54%), which corroborates the observations of Czeizel and Ludanyi [1985], who reported that 70% of their VACTERL cases were male.

The proposed risk to sibs of patients with TEF has been estimated at 1% [Skinner, 1990; Pletcher et al., 1991]. Of 347 known sibs in our study, only 1 exhibited esophageal atresia without TEF (0.3%). Five of 347 sibs (1.4%), including three sets of twin sibs, showed other VACTERL malformations. No sib showed more than one VACTERL malformation, and no index patient had more than 1 sib with a VACTERL-related malformation. David and O'Callaghan [1975], in reviewing sibs of patients with EA, found that 1 sib in 365 (0.27%) had EA. However, it was later discovered that this family had 3 sibs with EA and laryngeal fissure. The parents were unaffected; thus, this family may have had a rare autosomal-recessive condition. Warren et al. [1979] found that 1 of 130 sibs (0.77%) had a TEF-related malformation (EA). David and O'Callaghan [1975] reported that there were nine instances of other VACTERL malformations among 365 sibs (2.7%) of individuals who had EA. It is unknown whether these nine malformations occurred in 9 different children. Czeizel and Ludanyi [1985] reported no recurrence of TEF or other VACTERL malformations in 120 sibs of 43 index patients who had the VACTERL association. Based on our data, we conclude that the recurrence risk for sibs of affected individuals to have TEF or EA is <1% (95% CI, 0–1.1%), and the risk for sibs to exhibit other VACTERL malformations is approximately 1.2% (95% CI, 0.3–2.6%). King et al. [1977] suggested that the cause of isolated TEF may differ from that of TEF which occurs as part of the VACTERL association. King et al. [1977] noted

TABLE III. Incidence of VACTERL Malformations in Parents

	n (%)
Parents with known medical history	252
Parents with renal malformations	4 (1.6)
Parents with congenital heart disease	1 (0.4)
Parents with any VACTERL malformations	5 (2.0)
Parents with no VACTERL malformations	247 (98.0)

TABLE V. Proportion of TEF or VACTERL Malformations in Children[a]

	n (%)
Living index patients with TEF	82
Living index patients who have had offspring	23
Total number of offspring of index patients	41
Number of TEF-affected children	1 (2.4)[b]
Number of children with other VACTERL malformations (horseshoe kidney)	1 (2.4)
Total number of children with any VACTERL malformations	2 (4.9)
Total number of children with no VACTERL malformations	39 (95.1)

[a]No patient who had reached reproductive age and had had children had died by the time of this study.
[b]TEF, congenital heart disease, radial ray anomaly.

that isolated TEF can exhibit a "familial tendency." In contrast, King et al. [1977] noted that when one family member has the VACTERL association, with the exception of one set of monozygotic twins, isolated TEF has not been reported to occur. Our one case of parent-to-child recurrence of TEF occurred in a parent with isolated TEF whose child exhibited TEF, a congenital heart defect, and a radial ray anomaly. Thus, we think that when the index patient has TEF alone, the risk to relatives is for TEF and/or VACTERL malformations. For the purpose of genetic counseling regarding recurrence of tracheoesophageal fistula, we recommend taking a careful family history, including questions regarding the occurrence of all VACTERL-related malformations in first- and second-degree relatives. This is especially important, since isolated and VACTERL-related cases of TEF cannot currently be differentiated by cytogenetic or other laboratory genetic tests. Nearly half of patients with TEF will exhibit other VACTERL malformations. Regardless of whether or not other VACTERL malformations are present in a TEF-affected individual, the recurrence risk of TEF is <0.5% for sibs, and 2.4% for children.

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